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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/463,904	06/05/95	PHIPPS	J ARC-2399

EXAMINER

QM31/0402

ROCKEL MAN, M

ART UNIT	PAPER NUMBER
3734	18

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DATE MAILED: 04/02/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 10-24-97

☑ This action is **FINAL**.

☑ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-17 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-17 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

Response to Amendment

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Applicant and examiner had agreed to the entry of the claims as drafted in the after final amendment of 11-20-97. Applicant wished to further amend the claims and the examiner wished to further his arguments including potentially providing a new grounds of rejection in the case during the appeal process. After such agreement was reached, it was discovered by the examiner that he would no longer be permitted to raise such a new grounds due to the rule changes effective December 1, 1997. Thus, the examiner has elected to withdraw finality of the last office action, enter applicant's amendments and arguments, and accordingly apply the statutes and arguments seen fit so as to better present the issues to the Board for purposes of appeal.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Phipps et al '739 in view of Phipps '894.

Primary reference Phipps et al '739 teaches the delivery of fentanyl and sufentanil (column 13 line 50) in hydrogels (see last line of abstract) which may comprise an adhesive (column 6 lines 18-20). Applicant differs in reciting specific ranges of concentration for the medicaments fentanyl and sufentanil that, supposedly, render the drug flux independent of the concentration of the medicament in the reservoir. Secondary reference Phipps et al USPN 5,125,894 discusses the relationships between current intensity and density and drug concentration in general and how medicaments have a threshold level above which, a linear relationship exists between current levels and the amount of drug delivered. Phipps et al refer to the Padmanabhan article (a copy of which applicant has supplied in the response of 6-9-97) which demonstrates the relationship for a particular compound and system. Since Phipps '894 teaches that it was desirable to deliver medicaments above their threshold level (and supposedly even during the addition of extraneous ions) so that the amount of current can be utilized to control the rate of drug delivery over a sustained period of time. To have tested, determined and used the threshold levels for fentanyl and

sufentanil in a particular systems that include (or don't include) extraneous ions would have been an obvious optimization of parameters to sustain desired levels of drug flux.

It is noted that the examiner has changed his position slightly in regard to the explanation of his the rejection under art. The examiner had previously maintained theat applicant's claims were limited to the a linear region of operation.. While the applicant has been claiming that the fentanyl delivery is maintained at a constant level of drug concentration, at the claimed concentrations it could not be for a substantial period for the concentrations at the lower end of the claimed range.

According to the examiner's calculation:

with fentanyl mol wt = 336.36g/mol

11 mM fentanyl = (11 mMol/L) x (1mol/1000mMol) x (336.46g/mol) x (1L/1000mL)

= 3.7 mg/ml

As seen from applicant's graph in figure 2, this concentration corresponds to a region of about 20% efficiency. Slightly to the left or right of this point yields a substantial change in efficiency. Thus, for a proposed fentanyl delivery rate (see Haak et al. USPN 5,203,768 see column 14 lines 46-53) of 325 ug/hr and an initial concentration of 5mg/ml, a three hour delivery period would deplete the reservoir by 1 mg/ml, which would drop applicant's efficiency by half. Hence, applicant's drug flux would not be maintained for a constant current level output. Even a

one hour delivery would result in a substantial change in efficiency resulting in decreased flux. It is unclear what applicant is trying to cover with his claims.

5. Claims 1-17 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Haak et al USPN 5,203,768 (in view of Phipps '894). Haak et al provides working examples of fentanyl and sufentanil in a hydrogel which are stated to provide 25 ug of fentanyl and 5 ug of sufentanil every 5 minutes that the device is in activation. Since the device must act in a linear fashion for patentee to make this statement, it is inherent that the concentration is in the range claimed by applicant. Notwithstanding, a 10% concentration of fentanyl is incorporated into the patch. Thus, even if the gel, when hydrated, absorbs twice its weight in water, the concentration of fentanyl will still be 1% of the solution and three times the minimal concentration provided by the claim. Since applicant appears to have a common assignee and have access to these gels the examiner requests hydration data and other related material that may provide information about the drug concentrations in these examples. Haak teaches that the device is turned on during episodes of pain (i.e. turned on and off), thus a "substantial" portion of the drug remains in the reservoir when the device is intermittently turned off. If not inherent, it would have been obvious in view of Phipps "894 to have operated the device in the linear region for fentanyl which would inherently include at least a portion of applicant's claimed range.

It is noted that buffering the solutions is considered an option (see column 6, lines 1-8)

Response to Arguments

6. Applicant's arguments filed 11-20-97 have been fully considered but they are not persuasive. The examiner outlines his reasoning below:

I. Applicant's Claims are Now Limited to Iontophoresis

First, the examiner notes applicant's discussion of the Weaver, Sibalis and Levy references on pages 3-4 paragraphs 1 and 2 in the response of 11-20-97. Applicant sums up the examiner's position by stating that apparently the examiner feels that "unexpected" results provided in the evidence of record were based upon iontophoretic trials. The examiner does not recall stating or implying that applicant showed "unexpected" results and hence the examiner clarifies his position by stating that the *only* results demonstrated by applicant were during iontophoresis trials. Whether the applicant's results are "unexpected" or not remains an issue. Since applicant only demonstrated results using iontophoresis, it was not understood how applicant could argue "unexpected" results for a claim that encompasses "electroosmosis" or, more so, "electroporation". The examiner does not contend that the results "could not be applied to the mechanisms". While the other modes of delivery have mechanisms that are different from iontophoresis, the examiner would consider them obvious alternative mechanisms to try, and routinely experimented on so as to optimized. However, if applicant is arguing unexpected results (see applicant's response, paper # 12 page 6 lines 3-8), the studies must be commensurate in scope with the breadth of the claims. In this case, prior to amending, applicant's claim scope

included methods that were purely electroporation or electroosmosis without showing any relationship between these modes of delivery and the specific concentrations claimed. It was unclear if these alternative mechanisms would be optimized in the same drug concentration ranges as that for iontophoresis and as claimed.

Secondly, the argument of the Weaver, Sibalis and Levy references is a moot point since the claims are now limited to iontophoresis, where closer art is found.

II The Phipps 1.132 Declaration

Beginning at page 5 paragraph 2 of applicant's response, applicant has provided further explanation in regard to the Phipps 37 CFR 1.132 affidavit filed on 6-7-97. In response, the examiner readdresses that declaration prior to addressing applicant's most recent comments.

The arguments advanced by Dr Phipps do not pointedly counter the rejections made by the examiner because they do not address the Phipps '894 reference. In addition, applicant also does not provide evidence supporting his allegations and ignores the '894 Phipps reference totally in the rebuttal.

The Phipps argument can be summarized as follows:

1. Phipps states that the drugs claimed in this invention are potent and overdosing is a concern.

2. Rates of diffusion can be decreased by decreasing the concentration applied to the skin.

3. Low concentrations have been desired to minimize diffusion.

4. It is desired that the drug reservoir contain only the amount of drug needed for treatment of the patient.

5. To "demonstrate" that the prior art does not teach his invention Dr Phipps cites a passage from the Padmanabhan reference (which states that the steady state delivery of the drug is not affected until the drug concentration falls below a given value) and then "contrasts" his invention by stating that he uses drug concentrations that operate such that the flux is independent of drug concentration.

6. In support of his position , Dr Phipps points to a theoretical example provided by Casting and Caster for modeling delivery.

7. Finally, Dr Phipps restates the objectives of his invention, to provide a drug reservoir that is not fully depleted and maintains a steady flux during delivery.

A. The Phipps 1.132 affidavit provides has no convincing basis or evidence in support of their conclusion.

The "basis" that applicant asserts for unobviousness is that one of ordinary skill in the art of iontophoresis would have been concerned about overdosing by passive drug flux. Such a premise is without merit. For overdosing to occur, a certain amount of drug must be contained in the reservoir and must be administered over a specified time period. Applicant does not claim an amount contained in his reservoir, only a concentration. It is possible to have a high concentration

of drug, but an insufficient amount to cause overdosing. Notwithstanding, neither applicant nor the prior art demonstrate if overdosing is even possible using the salt forms of fentanyl and suffentanil by passive transdermal application much less concentrations and amounts approaching dangerous levels. Why would one be concerned about overdosing at a concentration in the range of 10mM. The Gale et al USPN 4,588,580 patent seems to teach the contrary. It is stated therein that in the context of passive delivery, that fentanyl citrate has low skin permeability for transdermal delivery. Table 3 of the same reference teaches the formation of passive components with up to 50% (i.e 50mg/ml) of the most soluble form, fentanyl base.

In sum , the evidence of record seems to contradict applicant's premise rather than support it. In addition, applicant provides no protection (i.e rate controlling membrane) against overdosing in the claims and has a concentration range without an upper limit which raises questions about as to whether applicant himself shows any concern for overdosing.

B. The 1.132 affidavit filed by applicant does not address the '894 reference for what it says and therefore does not constitute a proper rebuttal

The '894 patent provides both the motivation to seek linearity between amounts of current and the amount of drug to be delivered and provides instruction to the reader to accomplish this task by providing drugs in concentrations above their threshold levels (a level where extraneous ions compete). "The amount of current can be utilized to control the delivery" is stated on column 10 of the Phipps '894 patent providing motivation for seeking such linearity. The Phipps '894 patent also teaches that *in general* there is a threshold level at which a drug concentration

must exceed (in conditions of little or no extraneous ions) in order to observe linearity between amounts of drug delivered and the amount of current applied.(see column 11 lines 7-16). The examiner concluded that it would have been obvious to test the drugs fentanyl and sufentail used in the Phipps '739 patent for their threshold value and to maintain drug concentrations above such values for purposes of maintaining a constant flux and hence controlling the rate of delivery by the amount of current . The Phipps affidavit fails to disputes the premise or the conclusion of the examiner's rejection. Applicant neither disputes the fact that *in general* drugs exhibit a linearity above a threshold level nor disputes that it was known to operate iontophoresis devices in their linear range to control delivery rates. Dr Phipps does not discuss the statements made in his previous '894 patent at all and chooses to remain silent as to their content. As a result, the Phipps affidavit cannot be considered a persuading rebuttal to the examiner argument.

Applicant instead focuses on the particulars of the Padmanabhan, a reference which only comes into play as a demonstration of a particular example to support the Phipps '894 teachings.

C. Applicant's allegation that Padmanabhan teaches away from applicant's invention is illogical. Applicant appears to rely upon a faulty premise to draw his conclusion.

Rather than addressing the statements made in the Phipps '894 patent, Dr Phipps discusses the Padmanabhan reference, to which the Phipps '894 patent refers. The Padmanabhan

reference provides an example of a particular compound in a particular delivery system and demonstrates the existence of a linear operating region when drug concentration is above threshold value. The examiner considers this reference to be merely an exemplifying demonstration of the threshold level phenomena with the particular drug Hydromorphone used in a particular device.. As drug levels approach those in which competing extraneous ions take affect, linearity is lost. In addition, to this specific demonstration there is peripheral information that one notes concerning the level of skill in the iontophoretic art. Specifically, Padmanbhan shows that it was known to test compounds for their efficiency, as seen on page 129 of the Padmanabhan reference. The examiner notes that this is in alignment the examiner's position that testing compounds to optimize their delivery (i.e achieve linearity) is known and is obvious to one of ordinary skill.

The Phipps position in the 1.132 affidavit regarding the Padmanabhan reference is that because Hydromorphone steady state delivery was not significantly influenced until the drug concentration reached 1 mM, that it is surprising that the claimed concentrations of fentanyl and sufentanil in applicant's examples yield a drug flux independent of concentration at higher concentrations than Hydromorphone. The examiner does not follow applicant's logic. Different drugs will exhibit different threshold levels. These words come straight from applicant's own pen in his prior ('894) patent. Beginning at the last line of column 10 and extending to the next page "...and is above a threshold value determined *by physical/chemical properties of the transported species and tissue through which transport occurs*" (emphasis added). Given this, and of course

the consideration of the presence of extraneous ions in applicant's examples, it is not understood what lead applicant to the conclusion that he made. For applicant to have arrived at the conclusion that he reached he must have relied on a faulty premise that one particular chemical's threshold concentration would be the same as that of other compound. Notwithstanding, in reaching such a conclusion applicant must not have accounted for the fact that Padamanabhan used a sacrificial silver electrode (which does not generate extraneous ions) while applicant himself loaded his reservoir with NaOH at a concentration that appears to be at least a very influential 10 mM concentration. The '894 reference is based upon the addition of extraneous ions for varying drug flux. Why would applicant state that the results are unexpected? Applicant has merely provided the requisite testing of the compounds fentanyl and sufentanil under certain conditions

D. The applicant's conclusion that the Casting and Keister reference would influence one of ordinary skill in the art away from applicant's claimed invention is based upon a flawed premise.

Applicant argues that the Keister and Casting reference, beginning on page 202, would lead one of ordinary skill away from the claimed invention presumably because of the statement that "[efficiency] is independent of concentration in this example". The examiner notes that the statement that applicant extracts from the Casting and Keister reference when analyzed in its proper context is directed to a theoretical "example" which models the behavior of a drug in a

reservoir containing no NaCl (i.e no competing ions) in which the drug is transported through a simple ideal aqueous phase homogeneous membrane. As in the case of all models, while it is useful in explaining certain phenomena, it can not be relied upon for accurate predictions all behavior in general. In order for one of ordinary skill in the art to reach the conclusion applicant made, based upon the statement applicant quoted, one of ordinary skill in the art would have to rely on the premise that the Casting model absolutely represents the stratum corneum and predicts the behavior of drugs across the stratum corneum despite the delivery system used (i.e that the stratum corneum behaves exactly as Kastings example 1 even when ions are present in the reservoir). Such a premise is flawed as shown by the prior art. Phipps '894, Padamanabhan and even Casting himself would not rely on such a premise. All three authors note that competing ions affect transport efficiency Kastings states (page 206, see item (3)) that "the efficiency of drug delivery (i.e., the drug transference number tm can be maximized by minimizing or eliminating the number of small, mobile ions in the donor solution having the same charge as the drug. For positively charged drug this would mean minimizing or eliminating ions *like* Na^+ *and* K^+ in the donor solution" (emphasis added). With applicant adding NaOH to buffer his reservoir in concentrations of at least 10mM, what would lead applicant to believe that Kastings teaches away from applicant's results. Phipps '894 uses this influence on the addition of extraneous ions to regulate the efficiency of drug delivery. The examiner believes one of ordinary skill in the art would have expected threshold level drug concentrations to be different for different drugs based

upon the Phipps '894 teaching and, when buffered with Na OH, to be higher than usual based upon the teachings of both the Phipps '894 and the Casting and Keats references.

III Applicant's latest Response

In applicant's latest response, the examiner notes that (page 4 second paragraph) that applicant notes that concentration and amount are two different considerations when it comes to overdosing. The examiner agrees. As noted before, this is a true statement and renders applicant's premise of "overdosing concerns" as discussed above in section A faulty. In regard to the applicant's further explanation of the Phipps declaration, the examiner refers applicant to the above analysis. Contrary to applicant's reassertion, the prior art does suggest applicant's invention rather than teach away from it. The examiner takes issue with applicant's statement beginning at the bottom of page 6 last line to the next page. As applicant is well aware, the Theeuwes et al USPN 5,232,438 is currently under reexamination since the patentees claimed "fentanyl" from a long list of drugs that were "anticipated" to work and drafted claims to methods of anesthetizing patients. To support the claims a piecemeal analysis of the specification and reliance on the knowledge of the skilled artisan is needed for support. For the examiner to likewise extract portions of a document to demonstrate the invention being taught is fair game. Nonetheless, the reference was relied upon as a base reference as a showing that hydrogels were well known reservoirs and fentanyl was a well known drug useful in the iontophoresis art. To

further make this showing, the examiner has relied upon Haak et al 5,203,768 to provide a specific example of the combination.

Finally, the examiner notes that apparently the applicant feels that part of his invention is the termination of drug delivery while a substantial portion of the drug remains in the reservoir. The examiner argues that one must also retain a substantial portion in the reservoir because it is difficult to entirely deplete the reservoir as noted by Padmanabhan. Secondly, the reference applied all wish to operate only in the linear region so that accurate dosing takes place. Therefore, it is obvious to the two Phipps references, and believed to be inherent to the Haak et al reference(which seeks to treat multiple episodes of pain) to terminate delivery after the desired dosage has been administered.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Bockelman whose telephone number is (703) 308-2112. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Wynn Wood-Coggins, can be reached at (703) 308-1344. The main fax phone number for this Group is (703) 305-3590. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0858. Please note that after April 1, 1998 Art Unit 3306 will become Art Unit 3734 due to PTO reorganization. Please indicate Art Unit 3734 as the mail destination in all future correspondences directed to this application.

Mark Bockelman
MARK BOCKELMAN
PRIMARY EXAMINER

MWB

April 1, 1998